IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Application No. 10/526,780
Akihiko KITAJIMA et al.
Filed: May 20, 2005

Confirmation No. 8813
Group Art Unit: 1614
Examiner: Phyllis G. Spivack

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents and Trademarks

Sir,

I, Toshiharu YANAGI declare that:

I was born in Tokuyama city, Yamaguchi Prefecture, Japan, on December 18, 1966;

I am a citizen of Japan and a resident of c/o Kobe Product Development Center, Nagase ChemteX Corporation, 2-2-3, Murotani, Nishi-ku, Kobe city, Hyogo 651-2241, Japan;

I graduated from Yamaguchi University, Faculty of Science, Department of Chemistry in 1989;

I received Master of Science from Nagasaki University, Faculty of Pharmaceutical Science in 1991;

I received Ph.D. from Okayama University, Faculty of Pharmaceutical Science in 2000. My doctoral work dealt with the development of a new drug candidate entitled "Synthesis and Pharmacological Activities of a new gastrokinetic agent 4-Amino-5-chloro-2-methoxy-N-[(2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl]benzamide (TKS159)";

I have been an employee of Nagase ChemteX Corporation, Japan, since 1991 up to this time;

At present, I am a general manager of Bulk Pharmaceuticals Division, Bio/Fine Chemicals Department in Nagase ChemteX Corporation in 2006;

I reported the following papers, for example;

1. Pharmacological Activity and Structural Analysis of a Benzamide (TKS159) and Its Optical Isomers in an *In Vitro* Study and an *In Vivo* Study in Mice.
   Mizoguchi, Jun-ichi; Yanagi, Toshiharu; Anzai, Kinsei; Kodama, Kazuya; Kamoda, Osamu; Kamei, Chiaki; Kanehisa, Nobuko; Kai, Yasushi; Wada, Takehiko; Inoue, Yoshihisa.
   Methods Find. Exper. Clin. Pharmcol., **2007**, 29(3): 199-203.
2. Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid Using a Chiral N-(2-Hydroxymethyl-4-pyrrolidinyl)benzamide Template.
   Mizoguchi, Jun-ichi; Kawanami, Yuko; Wada, Takehiko; Kodama, Kazuya; Anzai, Kinsei; Yanagi, Toshiharu; Inoue, Yoshihisa.
   Org. Lett., **2006**, *8*, 6051-6054.
3. *In Vitro* Antibacterial Activity of a Novel Antimicrobial Agent TG44 for Treatment of Helicobacter pylori Infection.
   Kamoda, Osamu; Anzai, Kinsei; Mizoguchi, Jun-ichi; Shiojiri, Masatoshi; Yanagi, Toshiharu; Nishino, Takeshi; Kamiya, Shigeru.
   Antimicrob. Agent Chemther., **2006**, *50*, 3062-3069.

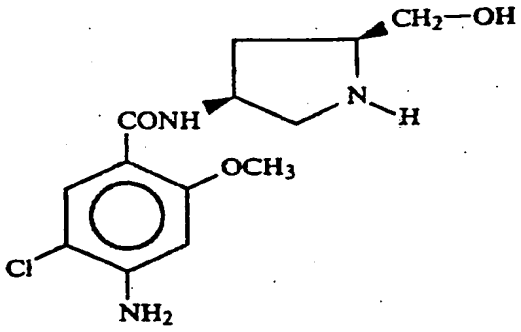
1. Tested compounds

(1) The compound of the present invention

4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide

(hereinafter referred to as TM161)

TM 161

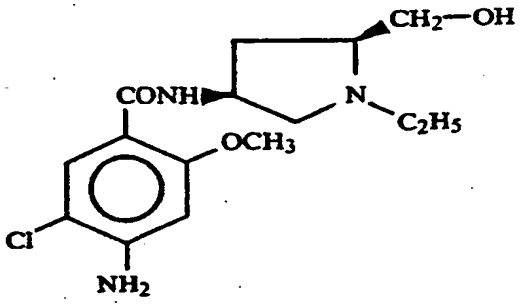


(2) Comparative compound

4-amino-5-chloro-2-methoxy-N-[(2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl]benzamide

(hereinafter referred to as TKS159)

TKS 159



2. Side-effect

Corpus striatum extracted from a Wister male rat was homogenized in a 50 mM Tris-HCl buffer, and centrifugation and suspension were repeated to prepare a dopamine D_2 receptor sample. The receptor sample was reacted with a solution containing a 0.25 nM radioactive ligand of [^{3}H]-spiperone and TM161 at a prescribed concentration.

The same experiment as mentioned above was conducted using TKS159 in place of TM161.

The binding with a dopamine D2 receptor is one of causes of side-effect, such as extrapyramidal sign.

Test compounds	IC_{50} μM
TM161	34
TKS159	3.8

Binding affinity for a dopamine D_2 receptor of TM161 is weaker 8.9 times as much as that of TKS159.

3. Safety

TM161 was repeatedly administered orally to three beagle dogs at a dose of 100 mg/kg once a day for 4 weeks.

Pathohistological test was performed using a light microscope. Abnormality was not seen in a pathohistological test, and thrombus formation, arteritis and encephalomalacia were not recognized.

On the other hand, TKS159 was repeatedly administered orally to two beagle dogs at a dose of 30 mg/kg once a day for 4 weeks.

Pathohistological test was performed using a light microscope. Abnormality was not seen in a pathohistological test, and thrombus formation, arteritis and encephalomalacia were not recognized.

TKS159 was repeatedly administered orally to two beagle dogs at a dose of 100 mg/kg once a day for 4 weeks.

Pathohistological test was performed using a light microscope. Abnormality was seen in a pathohistological test, and thrombus formation, arteritis and encephalomalacia were recognized.

The safety as to thrombus formation, arteritis and encephalomalacia of TM161 is bigger 3.3 times as much as that of TKS159.

It is declared by the undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 20th day of December, 2007

Toshiharu Yanagi

Toshiharu YANAGI